Neurological Manifestations and Neuroimaging Findings of Acute Intermittent Porphyria Patients

jian cao
Peking Union Medical College Hospital
fei han
Peking Union Medical College Hospital
qianlong chen
Fuwai Hospital State Key Laboratory of Cardiovascular Disease
hui you
Peking Union Medical College Hospital
tienan zhu
Peking Union Medical College Hospital
yongqiang zhao
Peking Union Medical College Hospital
xuezhong yu
Peking Union Medical College Hospital
huadong zhu
Peking Union Medical College Hospital
jing yang (yangbujing@126.com)
Peking Union Medical College Hospital (Dongdan campus), No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing,China https://orcid.org/0000-0002-8334-9034

Research

Keywords: acute intermittent porphyria, neuroimage, hyponatremia

Posted Date: September 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-77039/v1

Abstract

Background: Acute intermittent porphyria (AIP) is an inherited disorder of heme biosynthesis, a porphyric attack can affect the autonomic, peripheral, and central nervous systems. The neurological clinical manifestations of which are incompletely understood. The neuroimaging findings of AIP could be reversible.

Methods: In this report, we describe 29 cases of AIP, focusing on neurological clinical features and neuro-imaging. **Results:** In this study, we showed two cases of PRES, two cases of ODS, two cases of porphyric encephalopathy (cortical laminar necrosis), one case of RESLES. We divided 29 cases into 2 groups ,the blood sodium levels of who with MRI/CT abnormality were significantly lower than which with normal MRI/CT(110±43.15mmol/L and 117±57.02mmol/L, p=0.01).

Conclusions: To the best of our knowledge, these are the biggest series of MRI in AIP in China, and the only published cases of ODS associated with AIP in China. Hyponatremia may be an important mechanism in porphyric encephalopathy.

Background

Acute intermittent porphyria (AIP) is a rare autosomal dominant inherited disorder characterized by a partial deficiency of porphobilinogen deaminase (PBGD), the third enzyme in the heme biosynthetic pathway. Most AIP patients are no symptoms except for acute intermittent attacks. Such attacks are characterized by diverse symptoms including abdomen pain, tachycardia, hypertension, unawareness, seizures and psychiatric symptoms[1, 2]. There are just a few reports of the neuroimaging findings in AIP patients with acute neurologic manifestations including seizures. The performance of brain MRI of AIP is diverse. Posterior reversible encephalopathy syndrome (PRES) is associated with potentially reversible neuroradiological abnormalities predominantly in the parieto-occipital lobes. Osmotic demyelination syndrome (ODS) refers to central pontine myelinolysis and extrapontine myelinolysis. Reversible splenial lesion syndrome (RESLES) is a clinico-radiological syndrome characterized by the presence of reversible lesions specifically involving the splenium of the corpus callosum (SCC). Many of these studies have suggested that MRI changes were related to PRES[3–5]. The relationship of the neurological manifestations and neuroimaging findings of AIP is not well understood. Here, we describe 29 cases of neuroimaging findings of AIP with neurological symptoms.

Patients And Methods

From January 2013 to July 2019, a total of 69 patients were diagnosed with AIP in the emergency center of our hospital. The following diagnostic criteria were used: 1) acute attack symptoms and 2) positive for urine porphobilinogen (PBG). We conducted a retrospective analysis of these patients. 29 of 69 had neurological symptoms (convulsion, confusion, difficulty swallowing etc). We collected information about ethnicity, past medical history, clinical features, neuro-imaging, medications, treatment, investigations and outcome of these 29 patients. Among 29 patients 26 agreed to have genetic testing for porphobilinogen deaminase (PBGD) gene mutations. We did the genetic screening tests of AIP in these families.

Qualitative screening tests of urinary PBG (Watson-Schwartz method)

Urine porphobilinogen (PBG) was quantitatively screened using the Watson-Schwartz method. Briefly, urine was added to Ehrlich's reagent (0.7 g dimethylamine broane dissolved in 150 mL concentrated hydrochloric acid and 100 mL water). After 1–2 min, a saturated sodium acetate solution was added, and the non-specific colors were removed by extraction with chloroform and n-butanol. A positive PBG result was indicated by a distinct pink color in the lower layer[6].

CNS Studies

During porphyric attack, brain CT and/or MRI was performed on most (25/29) patients with CNS symptoms or headache, while electroencephalography (EEG) was performed on some (5/29) patients, CSF test was performed on (7/29) patients.

Genetic testing

The molecular genetic analysis of the HMBS gene was performed by direct sequencing of peripheral blood sample. All 14 exons of the PBGD gene and a minimum of 20 base pairs of flanking intronic DNA for each exon were amplified by polymerase chain reaction (PCR) (Tiangen Biotech, Beijing, China) and subsequently sequenced using the BigDye Terminator Cycle sequencing kit version 3.1 (ABI Biosystems) on an ABI PRISM 3730 Sequence Analyzer according to the manufacturer's instructions. We aligned the sequences by Chromas software and ncbi website (http://blast.ncbi.nlm.nih.gov/Blast.cgi) to identify variations. We also annotated the filtered variants as "known" or "novel", depending on whether they had been previously reported in the 1000 Genomes Project (http://www.1000genomes.org/data)

All methods were performed in accordance with the relevant guidelines and regulations.

Results

The demographics, disease course, clinical features and of these 29 AIP patients are summarized in table I. The patients had a disease history ranging from 4 days to 6 years. Acute attacks were accompanied by gastrointestinal symptoms in 28 patients. 29 patients all exhibited neurological manifestations, including consciousness disturbance (n = 25), convulsion or seizure (n = 21), and muscle weakness (n = 7). 3 of the 29 patients exhibited impairment of bulbar and respiratory function. 29 patients all had a documented history of hyponatremia (97–127 mmol/l). 12 patients had MRI/CT abnormality.

Results for electrophysiology and radiological studies, and molecular genetic analysis are summarized in table II.

We divided 29 patients into 2 groups, group 1(MRI/CT abnormality), group 2(MRI/CT normal), there are significant differences in blood sodium levels between the two groups ,[Na]of group 1(110 ± 43.15 mmol/L) lower than group 2(117 ± 57.02 mmol/L, p = 0.01).

MRI scans of Case 8 (14th day after onset) showed abnormal signals in the cerebral cortex, which were isointensity on T1W1 images, hyper-intensity on T2W2. (Fig. 1A and B). The cranial MRI performed 11 days

later revealed that the lesions determined on the first MRI were enhanced on contrast-enhanced axial T1-weighted MRI (Fig. 1C, D and E), repeated brain MRI at 10 months showing that the gyriform cortical lesions larger than before (Fig. 1F and G). Case 6 also had the same abnormal signals located in the cerebral cortex as case 3, but case 6 wasn't followed up.

The initial brain MRI of Case 20 revealed hyperintense gyriform lesions on fluid-attenuated inversion recovery (FLAIR) images (Fig. 3A and B). The cranial MRI performed 40 days later revealed that the lesions determined on the first MRI were significantly regressed (Fig. 3C and D, respectively). MRI findings of Case 9 just like Case 6.

Brain MRI of Case 16 revealed central pontine and extra pontine myelinolysis on FLAIR images (Fig. 2A and B). The cranial MRI five months later revealed that the lesions determined on the first MRI were significantly regressed (Fig. 2C and D, respectively). MRI findings of case 2,16 and 27 all diagnoses as ODS, but case 2 wasn't followed up, case 27 aggravated after 18 days .

Due to the lack of hemin in China, only supportive treatments could be administered, including high carbohydrate intake (250–300 g of glucose per day), fluid restriction (< 2000 ml per day), and avoiding suspicious drugs.

Sequence analysis of the PBGD gene identified 25 mutations in 25 patients are summarized in table 2 (3 patient didn't make detection). There were nine missense, four nonsense, seven splicing mutations, two aberrant splice site mutations.

More details of case 9 and case 28 have been previously published.

Discussion

Porphyria is a collective name of seven different diseases that are caused by an enzyme deficiency that inhibits the synthesis of heme. AIP is one of four forms of acute porphyria, which is caused by an inherited deficiency of PBGD. Symptoms of AIP occur during intermittent attacks are caused by the excess production of porphyrin precursors in the visceral, peripheral, autonomic, and central nervous systems, and may be life threatening.

Neurological manifestations of AIP include epileptic seizures, impaired consciousness, behavioral changes and hyponatremia maybe caused by inappropriate antidiuretic hormone syndrome [7, 8]. Peking union medical college hospital reported the characteristics of 36 Chinese patients with acute porphyria in 2016; 12 patients experienced neurological symptoms involving the CNS (12/36 confusion, 10/36 convulsion, 2/36 rapid progression to acute respiratory insufficiency)[7]. The prodromal symptoms in these cases included abdominal pain, muscle weakness. The weakness in case 9 and 15 progressed rapidly to quadriparesis and acute respiratory insufficiency, resulting in the delayed diagnosis.

The pathophysiology of the nervous system involvement of AIP patients is not very clear. Most reports of the neurological manifestations and brain imaging findings of AIP have been restricted to a single or small number of cases[8–10]. In vivo studies in mice have suggested that multiple mechanisms leading to the

varied symptoms, including interactions between 5-Aminolevulinic acid (ALA) and gamma-Aminobutyric acid (GABA) receptors and possibly heme depletion in nerve cells[9]. However, some findings in AIP patients have suggested that the relationship between the severity of neurological manifestations and the ALA/PBG levels is little[10]. In mainland China, tests of ALA and PBG levels are unavailable, it had been found that the serum sodium concentration was significantly negatively correlated with convulsion in our clinical studies[7]. These findings may reveal many factors contributing to the neurological manifestations of AIP. In 2011, the Chang Gung Memorial Hospital in Taiwan reported 12 cases of AIP; 9 patients experienced neurological symptoms involving the CNS (8 consciousness disturbance, 4 convulsion/seizure, 1 behavioral change). Among 4 patients who underwent brain MRI, 3 showed normal results, and 1 showed PRES, and this lesion recovered after 1 year[10]. In our study, 29 patients experienced CNS neurological symptoms, among 20 patients who underwent MRI, 9 showed MRI abnormality (2 PRES,4 ODS, 3 porphyric encephalopathy,1 RESLES).

The porphynic encephalopathy are believed to be most likely due to transient ischemic cerebral changes, although specific mechanism is unknown[11, 12]. These porphynic encephalopathy showed cortical and subcortical increased signal and gyriform diffuse enhancement[11–13].Our case 6 and 8 (Fig. 1) had similar cerebral abnormalities, case 8 had been followed by 3 MRI though 10 mons, showed consistent cerebral abnormalities, case 6 wasn't followed up.

Even though there are only a handful of PRES has been reported in AIP patients, it is by far the most common MRI abnormalities in AIP[3, 4, 9, 10]. In these cases, transient changes were observed in the cerebral cortex on MRI. Usually, these lesions are partially or completely reversible, symmetrical cortical and subcortical involvements of the occipital and parietal lobes, without or with mild enhancement, as observed in case 20 (Fig. 3). The most widely accepted hypothesis of the pathophysiology of PRES is the hyperperfusion theory[14]. The mechanism of PRES in AIP has been suggested to be mediated by hypertension due to autonomic dysfunction[5]. Case 20 progressed to dysphoria, confusion and severe hyponatremia after being diagnosed with "pregnancy-induced hypertension." However, our first patient with PRES in AIP (case 9) remained normotensive throughout, but she also had severe hyponatremia. Cases of PRES secondary to hyponatremia are rare in the literature[5, 15], little is known about the influence of hyponatremia on cerebrovascular regulation.

ODS refers to central pontine myelinolysis and extrapontine myelinolysis. These disorders are characterized by insults to regions of the brain with anatomical features predisposing white matter tracts to myelin injury in the setting of osmotic disturbances and their attempted correction[16]. Although many AIP patients have hyponatremia[7], ODS in AIP has been rarely previously reported[13]. Case 2,5,16 and 27 are first reported cases of AIP with ODS in China. These two patients had severe hyponatremia, which was quickly corrected before she experienced confusion or frequent convulsion. After three weeks, MRI of case 5 showed typical central pontine myelinolysis and extrapontine myelinolysis, as shown in Fig. 2. The clinical outcome of ODS was thought to be universally devastating[16], but case 5 completely recovered, and the MRI lesions regressed (Fig. 2). The MRI lesions of case 2 after 2 weeks no changed to the first time.

All 29 cases we reported showed severe hyponatremia, and it was found that the serum sodium concentration was significantly negatively correlated with convulsion before[7]. Blood sodium levels of who with MRI/CT abnormality were significantly lower than which with normal MRI/CT(110 ± 43.15 mmol/L and

117 ± 57.02 mmol/L, p = 0.01).We suggest that hyponatremia may be not only a clinical feature of AIP but also an important mechanism in porphyric encephalopathy. An increase in vasopressin levels occurs in hyponatremia[5]. Vasopressin facilitates the movement of water molecules into cerebral cells independently of hyponatremia by reducing the use of cerebral oxygen. Hyponatremia therefore plays an important role in cerebral edema. More research is needed in the future to prove this hypothesis. Because hyponatremia is a common feature in AIP, the rapid correction of hyponatremia should be avoided to prevent ODS.

Conclusion

In summary, the pathophysiology of the neurological manifestations in AIP patients is not well understood, cortical laminar necrosis, PRES, ODS and RESLES can all exhibit CNS involvement in AIP. Additionally, hyponatremia may be important mediators in the mechanism of porphyric encephalopathy.

Abbreviations

AIP
Acute Intermittent Porphyria
MRI
magnetic resonance imaging
PRES
Posterior reversible encephalopathy syndrome
ODS
Osmotic demyelination syndrome
RESLES
Reversible splenial lesion syndrome
SCC
splenium of the corpus callosum
PBGD
porphobilinogen deaminase gene
HMBS
hydroxymethylbilane synthase
FLAIR
fluid-attenuated inversion recovery images
T2WI
T2-weighted images
T1WI
T1-weighted images
ADC
apparent diffusion coefficient
CSF
cerebral spinal fluid
PCR

polymerase chain reaction

Declarations

Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975 (revised in 2000). The study protocol was approved by the Ethics Committee of the Institutional Review Board at Peking Union Medical College Hospital (PUMCH). A written consent form, stating acceptance of genetic testing, was signed by the patients and their family members.

Conflict of Interest

The authors declare that they have no conflict of interest.

Contribution list:

Substantial contributions to conception, design and writing: JC and JY.MRI image analysis: FH, HY and JC. Gene mutation detection: QC. Drafting the article or revising it: TZ, YZ, XY, HZ.

Funding

This study was supported by Tsinghua University-Peking Union Medical College Hospital Initiative Scientific Research Program□2019Z□.Manuscript writing were funded in this study. The funding bodies played no role in the design of the study, nor in the collection, analysis, or interpretation of the data.

Availability of data and materials

The data used and/or analysed to support the results of the current study are available from the corresponding author on reasonable request.

References

1. Floderus Y, Shoolingin-Jordan PM, Harper P. Acute intermittent porphyria in Sweden. Molecular, functional and clinical consequences of some new mutations found in the porphobilinogen deaminase gene. Clin Genet. 2002;62(4):288–97.

2. Karim Z, Lyoumi S, Nicolas G, Deybach JC, Gouya L, Puy H. Porphyrias: A 2015 update. Clin Res Hepatol Gastroenterol. 2015;39(4):412–25.
3. Kang SY, Kang JH, Choi JC, Lee JS. Posterior reversible encephalopathy syndrome in a patient with acute intermittent porphyria. J Neurol. 2010;257(4):663–4.
4. Lakhotia M, Pahadiya HR, Singh J, Bhansali S, Choudhary S, Jangid H. Posterior reversible encephalopathy syndrome as a rare presenting feature of acute intermittent porphyria. Neurol India. 2015;63(4):607–9.
5. Zhao B, Wei Q, Wang Y, Chen Y, Shang H. Posterior reversible encephalopathy syndrome in acute intermittent porphyria. Pediatr Neurol. 2014;51(3):457–60.
6. Buttery JE, Carrera AM, Pannall PR. Analytical sensitivity and specificity of two screening methods for urinary porphobilinogen. Ann Clin Biochem. 1990;27(Pt 2):165–6.
7. Yang J, Chen Q, Yang H, Hua B, Zhu T, Zhao Y, Zhu H, Yu X, Zhang L, Zhou Z. Clinical and Laboratory Features of Acute Porphyria: A Study of 36 Subjects in a Chinese Tertiary Referral Center. BioMed research international. 2016;2016:3927635.
8. Yang J, Yang H, Chen Q, Hua B, Zhu T, Zhao Y, Yu X, Zhu H, Zhou Z. Reversible MRI findings in a case of acute intermittent porphyria with a novel mutation in the porphobilinogen deaminase gene. Blood Cells Mol Dis. 2017;63:21–4.
9. Meyer UA, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. Semin Liver Dis. 1998;18(1):43–52.
10. Kuo HC, Huang CC, Chu CC, Lee MJ, Chuang WL, Wu CL, Wu T, Ning HC, Liu CY. Neurological complications of acute intermittent porphyria. European neurology. 2011;66(5):247–52.
11. Aggarwal A, Quint DJ, Lynch JP. 3rd: **MR imaging of porphyric encephalopathy**. AJR American journal of roentgenology. 1994;162(5):1218–20.
12. King PH, Bragdon AC. MRI reveals multiple reversible cerebral lesions in an attack of acute intermittent porphyria. Neurology. 1991;41(8):1300–2.
13. Susa S, Daimon M, Morita Y, Kitagawa M, Hirata A, Manaka H, Sasaki H, Kato T. Acute intermittent porphyria with central pontine myelinolysis and cortical laminar necrosis. Neuroradiology. 1999;41(11):835–9.
14. Maramattom BV, Zaldivar RA, Glynn SM, Eggers SD, Wijdicks EF. Acute intermittent porphyria presenting as a diffuse encephalopathy. Ann Neurol. 2005;57(4):581–4.
15. Eroglu N, Bahadir A, Erduran E: **A Case of ALL Developing Posterior Reversible Encephalopathy Secondary to Hyponatremia**. *Journal of pediatric hematology/oncology* 2017, **39**(8):e476-e478.
16. Alleman AM. Osmotic demyelination syndrome: central pontine myelinolysis and extrapontine myelinolysis. Semin Ultrasound CT MR. 2014;35(2):153–9.

Tables

Table 1 Clinical findings of these AIP patients with neurological symptoms

Patient	Age	Time to Dx (number of attacks)	Clinical features		serum Na (mEq/L)
			Neuological symtom	Non-neuological symtom	
1	F21	2 w	confusion, convulsion	Cyclical attacks, abdominal pain, constipation,	106
2	F22	6 m	confusion, convulsion	Cyclical attacks, abdominal pain,	110
3	F22	2m	Limb weakness		126
4	F24	2w	confusion, convulsion limb weakness	Cyclical attacks, abdominal pain,	113
5	F22	6 mons (2)	Weakness of lower limbs Involuntary activity Urinary incontinence	Cyclical attacks, abdominal pain,	112
6	F24	1 year (5)	confusion, convulsion	Cyclical attacks, abdominal pain, constipation,	114
7	F24		confusion	Cyclical attacks, abdominal pain, abnormal liver dysfunction	117
8	F23	11mon 2	Pains in the whole body, convulsion, urine retention	Cyclical attacks, abdominal pain constipation	115
9	F28	1mon 1	numbness of extremities, confusion, convulsion dysphagia, *dysarthria,* respiratory failure needed invasive mechanical ventilation	Cyclical attacks, *dark tea-colored urine*	120
10	F34		confusion, convulsion		112
11	F34		confusion, convulsion	Cyclical attacks, abdominal pain constipation	128
12	F21	5mon	confusion, convulsion and limb weakness	Cyclical attacks, abdominal pain constipation	127
13	F23	2mon	confusion, convulsion	Cyclical attacks, abdominal pain constipation	123
14	F21	4d	confusion	constipation	112
15	F27		Confusion,convulsion dysphagia/ respiratory failure needed invasive mechanical ventilation	Cyclical attacks, abdominal pain, constipation	116

16	F17	6mons (2)	Confusion,convulsion□dysphagia/ respiratory failure needed invasive mechanical ventilation	Cyclical attacks, abdominal pain, constipation□ vomiting	104
17	F22	6d	Confusion, convulsion□	abdominal pain, constipation□	106
18	F28	5 years □21□	Confusion, convulsion□	Cyclical attacks, abdominal pain, constipation□	108
19	F24	2mon	Confusion, convulsion□limb weakness	Cyclical attacks, abdominal pain, constipation□	119
20	F29	6mon	long lasting pain in the limbs and fatigue □dysphoria and confusion	Cyclical attacks, abdominal pain	108
21	F24	5years	Confusion, convulsion	Cyclical attacks, abdominal pain, constipation□	100
22	F35	7mon	Confusion, convulsion	abdominal pain, constipation□	113
23	F27	7days	Confusion, convulsion	Cyclical attacks, abdominal pain, constipation□	120
24	F24	11mon	limb weakness	Cyclical attacks, abdominal pain, constipation□	122
25	F30	6years	Confusion and limb weakness	Cyclical attacks, abdominal pain,	124
26	F29	2years	Confusion, convulsion	Cyclical attacks, abdominal pain, constipation□ hypertension	116
27	F19	1mon	Confusion, convulsion	Cyclical attacks, abdominal pain, constipation□	97
28	F20	7days □1□	sleepiness, confusion and then convulsion	abdominal pain, nausea, vomiting *and dark tea-colored urine*	119

Table II Summary of brain imaging findings, electrophysiological findings and molecular defects

Patient	EEG findings	CT findings	MRI findings	MRI follow-up (Time to 1st MRI)	Csf	mutation in *PBGD* gene
1	Negtive	Brain edema			Normal	Ala330Pro
2	Moderate abnormal		central pontine and extra pontine myelinolysis on FLAIR images		Normal	Trp283Term
3		Normal			Normal	
4		normal				
5			central pontine and extra pontine myelinolysis on FLAIR images	No change (2 weeks)		NO
6			T2-weighted shows predominantly cortical increased signal			c.613-1 G>A
7		normal			normal	
8			T2-weighted shows predominantly cortical increased signal	Aggravated 10days,lesions reduced to 1st MRI(10mons)		Trp283Term
9			hyper intense gyriform lesions on FLAIR images	regressed 6mons		Gln292fs
10			Normal			Arg173Trp
11		Normal				GLU209term
12			Normal			c.211-2G>A
13			Normal			c.88-1G>C
14			Normal			Glu250Gln
15			Normal			Arg173Trp
16			central pontine and	regressed 5mons		Lys70ASN

		extra pontine myelinolysis on FLAIR			
17	Low density of parietal lobe				c.210G>A
18		Normal			Ala219Pro
19		Normal			c.87+5G>T
20		hyperintense gyriform lesions on FLAIR images	regressed（40 days）		Gly218Glu
21	normal				I336Hfs*23
22	Brain edema			normal	c.912+1G>C(splicing)
23	Normal	Normal			c.826-1G>C
24		Normal			Arg173Trp
25		Normal			c.88-1G>C
26		Normal			Arg173Trp
27		central pontine and extra pontine myelinolysis on FLAIR	Aggravated （18days）		
28		isolated lesion of the SCC, with T2 and FLAIR hyperintensity, T1 hypointensity	regressed（15 days）		W198*

Figures

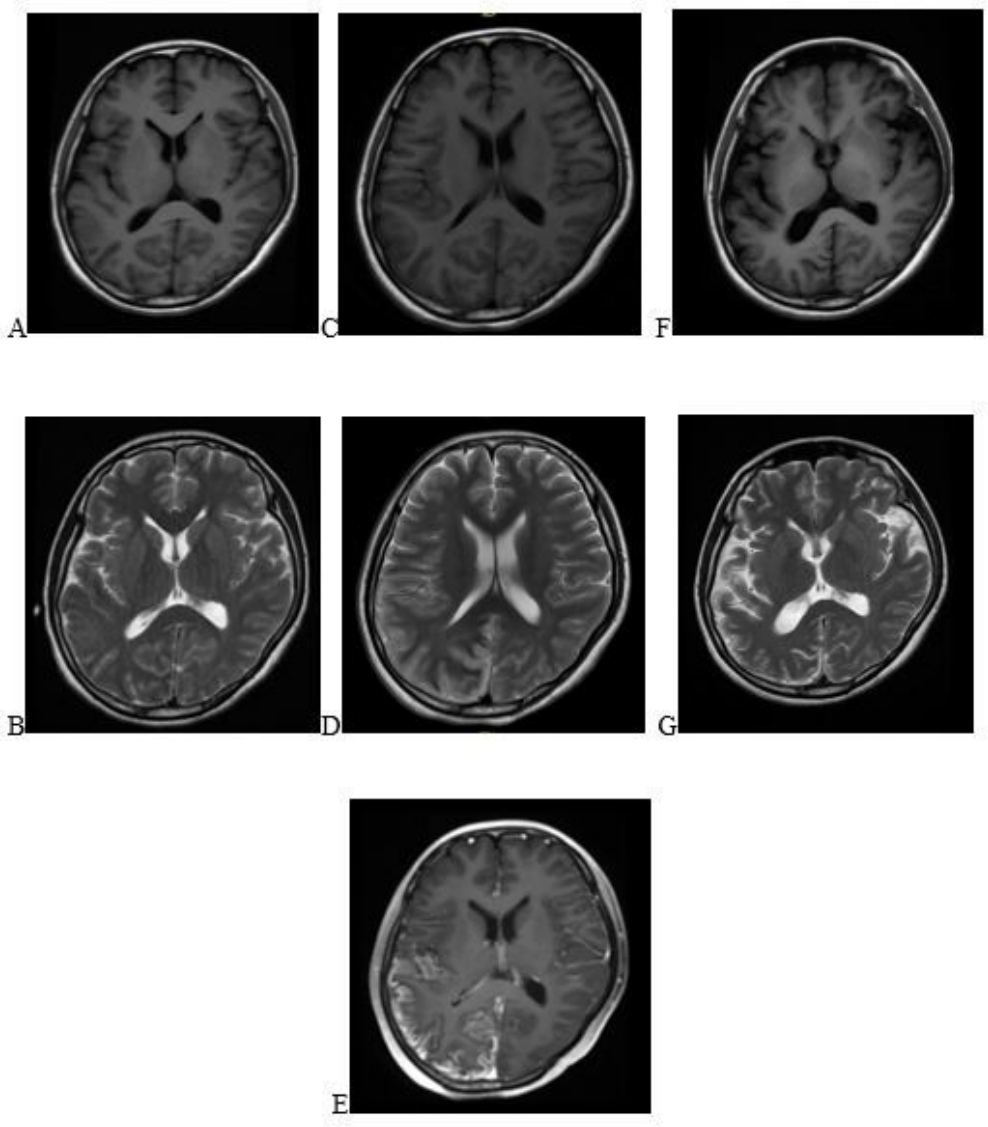

Figure 1

A,B MRI on 14th day after onset(2015-12-10),T2-weighted images showing high signal and isointense T1-weighted in cerebral cortex. C,D, E 25 days after onset(2015-12-21) , contrast-enhanced axial T1-weighted MRI, showing gyriform enhancement of the cerebral cortex. F,G Repeated brain MRI at 10 months(2016-10-31)showing that the gyriform cortical lesions larger than before.

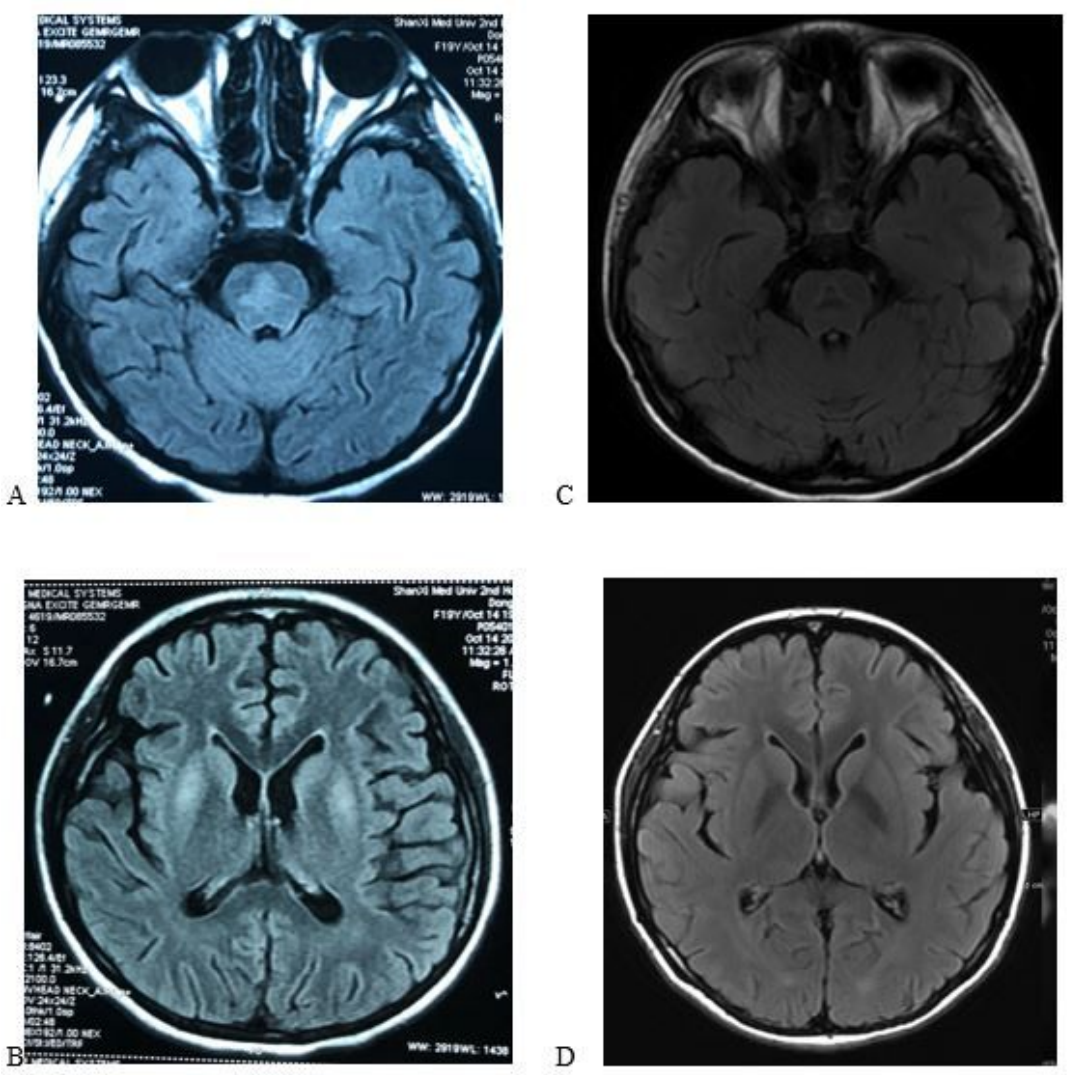

Figure 2

Axial fluid-attenuated inversion recovery (FLAIR) images (2017-10-14) showed (A) an hyperintense region in the central portion of pons (central pontine myelinolysis) and (B) symmetrical hyperintense signal in the putamen and caudate (extra-pontine myelinolysis). Repeated brain MRI at 5 month (2018-3-28) showed resolution of the hyperintensity in pons (C) and basal ganglia(D). Images show complete resolution of hyperintense lesions.

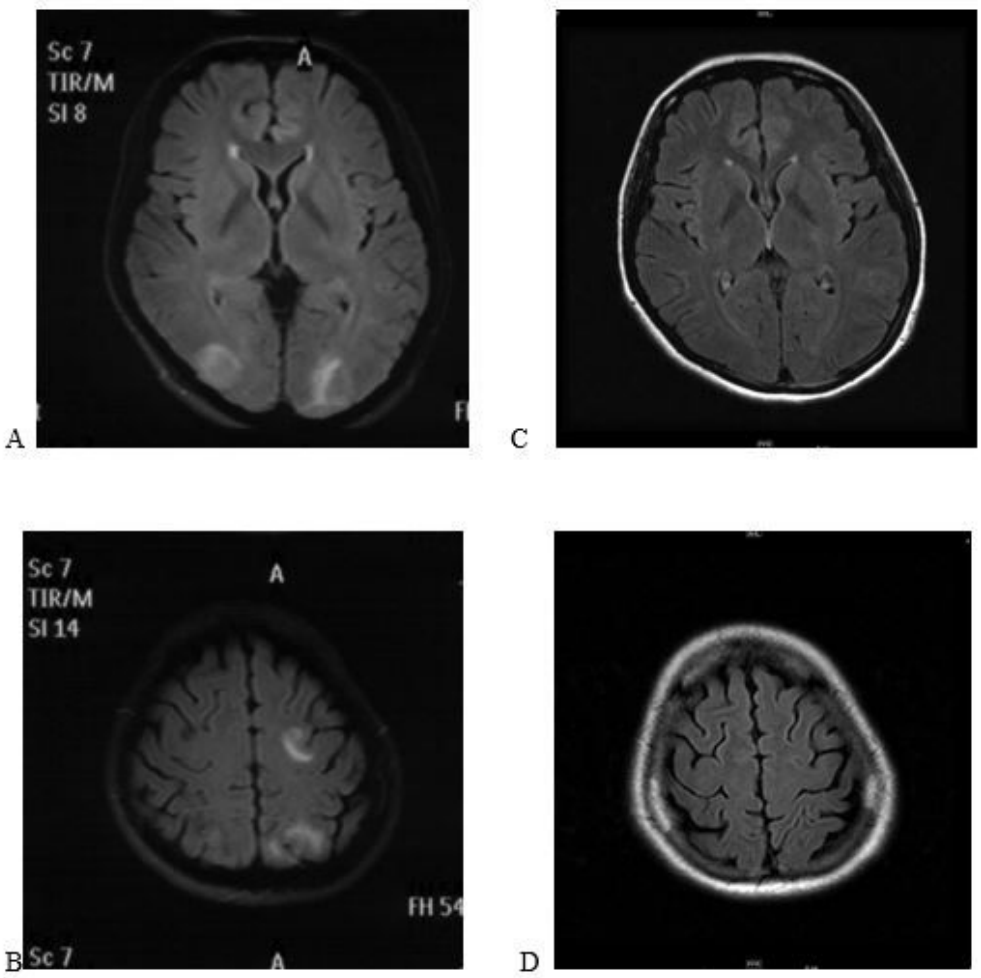

Figure 3

Axial fluid-attenuated inversion recovery (FLAIR) images (2017-12-18) show bilateral cortical and subcortical hyperintense lesions (A and B). Follow-up FLAIR (2018-1-18) images show complete resolution of hyperintense lesions (C and D)

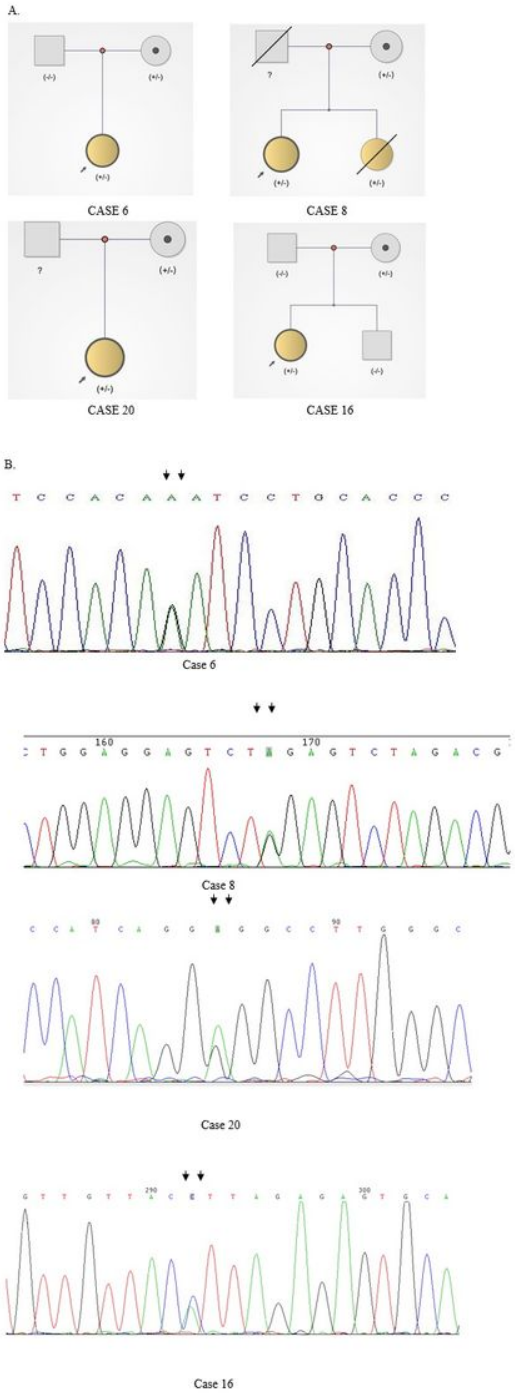

Figure 4

A novel PBGD gene frameshift mutation was identified in the family 6 and 20. A, 4 families pedigree with PBGD gene mutation (The arrow indicated the proband); B, Case 6, A novel PBGD gene mutation 10th intron splicing mutation c.613-1 G□A was identified in the proband and her mother; Case 8, a mutation c.848G>A (Trp283Term) was identified in the proband , sister and mother; Case 20, A novel PBGD gene mutation c.653 G□A (Gly218Glu) was identified in the proband; Case 16, a mutation c.210 G□T (Lys70ASN) and her mother